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Application No. 10/762,964
Filed: January 22, 2004
TC Art Unit: 1618
Confirmation No.: 6339

REMARKS

Claims 1-19 are pending. Claims 1-10 and 12-19 are rejected. Claim 11 is allowable except for its dependency on a rejected base claim. Claim 1 is amended herein.

Claim 1 has been amended to reword the claim for clarity. Specifically, the term "radio opacifying agent" has been replaced with "barium sulfate" in order to clarify the relationship with the antecedent, which is "barium sulfate" from the fourth line of the claim. No new matter has been added.

Claims 1-10 and 12-19 are rejected for alleged obviousness. The claim rejections are respectfully traversed. In view of the arguments presented below, all claims are believed to be allowable. Reconsideration of the rejections is hereby requested.

Rejections Under 35 U.S.C. 103(a)

Claims 1-4, 6-10, and 19 are rejected as allegedly obvious over Mueller et al. (DD238530A1, translation provided by USPTO) in view of Brown U.S. 3,236,735. Mueller is cited as allegedly disclosing a stabilized barium sulfate suspension comprising bentonite. The Office Action acknowledges that Mueller does not disclose solid formulations of barium sulfate. Brown is cited for teaching dry formulations of barium sulfate for use as X-ray contrast media.

Mueller's stabilized barium sulfate suspension is prepared by mixing 0.5-2.0% of barium sulfate with 3.0-6.0% of bentonite in water, stirring the mixture for 3 hours, then allowing it to settle for 3 days. Aside from the fact that Mueller does not

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TEL. (617) 542-2290
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teach solid formulations, the resulting suspension differs from the claimed invention in at least two important aspects: it fails to meet the required upper limit for ionic dispersants, and it fails to provide the required flocculating agent, as further discussed below.

The first difference between Mueller's formulation and the claimed invention is that Mueller's formulation possesses a higher concentration of ionic dispersants than permitted by the present claims, which are limited to less than 0.007 gram-equivalent weights of ionic dispersants per gram of barium sulfate. The reason is that Mueller uses a much higher concentration of bentonite than typically used in Applicant's formulation, and at such high concentrations the ionic components of bentonite are very significant. Contrary to the Examiner's assertion (Office Action at page 5, line 5), the Mueller formula is not free of ionic dispersant. Bentonite can carry a high electric charge and can act as an ionic dispersant. The exact electrical properties of bentonite vary depending on the source, but bentonite is invariably known to be ionic, in that it undergoes cation exchange in aqueous suspension. As stated for example in US 4,854,971, at column 3, lines 34-53, smectite clays such as bentonite have in the range of 50-150 meq/100g. Example 3, at column 5, lines 60-66 of the same patent, specifically illustrates a bentonite having 97 meq/100g. There is thus no doubt that bentonite is significantly ionic. Based on the high bentonite content of Mueller's formulation, a conservative estimate (see attached Appendix) is that it would contain at least 0.009 gram-equivalent weights of ionic material per gram of barium sulfate. Thus, Mueller's

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FAX. (617) 451-0313

formula lies outside the present claims, which limit the amount of ionic dispersants to less than 0.007 gram-equivalent weights of ionic dispersants per gram of barium sulfate.

The second difference between Mueller's formulation and the claimed invention is that Mueller does not provide a flocculating agent. During the three days of "settling" required by Mueller, certain physical and chemical changes are expected to occur in the bentonite, such that it no longer functions as a flocculating agent for barium sulfate. The purpose of the three day period is clearly to allow the bentonite to hydrate completely. In the hydration process, bentonite's tight laminar structure is destroyed by the interaction of layers of hydrogen-bonded water molecules. The resulting structure allows the original bentonite layers to slip over each other, producing a large increase in viscosity. The hydration step is essentially a chemical reaction whose end product is no longer bentonite. A person skilled in the art would be aware of such a change in the physico-chemical structure of bentonite during a three-day hydration period. Thus, in Mueller's barium sulfate suspension, bentonite no longer serves as the flocculating agent required by Applicant's claims; it serves instead to increase viscosity, so as to retard barium sulfate flocculation.

Another reason why Mueller's formulation is not flocculative is that the amount of bentonite used in Mueller much higher than in Applicant's formulation, as mentioned above. The amount of bentonite in Mueller's formulation is twice (i.e., 200%) the amount of barium sulfate used. An example of a formulation according to the present invention is that recited in claim 11,

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TEL. (617) 542-2290
FAX. (617) 451-0313

which contains 2% smectite clay and 95% barium sulfate. Compared to this example, Mueller uses about 100 times more clay than the present invention. There is no teaching or suggestion in any of the cited references that the amount of bentonite or stabilizing clay can be reduced 100-fold, to the point where the system becomes flocculative rather than stabilized, with the further expectation that the formulation is useful in certain types of imaging.

Furthermore, the requirement for a three day hydration period prior to its use as an X-ray contrast medium totally undercuts the alleged motivation to convert Mueller's suspension into a solid formulation, as described in the Office Action, and therefore undercuts any motivation to combine the teachings of Mueller and Brown. Mueller's disclosure teaches a liquid formulation that requires a lengthy and complicated preparation from its solid components. Therefore, if Mueller's suspension is to be spray-dried, as suggested in the Office Action for the alleged advantages of storing a solid formulation instead of a liquid one, it will have to undergo another three day hydration period in order to be reconstituted as a liquid formulation and to restore it to Mueller's intended stabilized state, otherwise the barium sulfate would precipitate. Further, it is unclear that the bentonite of Mueller's formulation, which undergoes physico-chemical alteration during hydration, and probably undergoes further changes during spray drying, would still be suitable to provide such stabilization after the hydration-drying-rehydration protocol suggested in the Office Action. Even if such a procedure would yield a suitable barium sulfate preparation, which is

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FAX. (617) 451-0313

doubtful, the extra steps and lengthy time of preparation would far outweigh any advantages of converting Mueller's formulation to a solid form, resulting in a preparation whose use would have no commercial viability. Therefore, Applicant asserts that there would have been no reasonable motivation whatsoever to combine Mueller's bentonite-stabilized barium sulfate suspension with the solid barium sulfate formulations of Brown.

Therefore, neither Mueller nor Brown, either alone or in combination, teaches or suggests a solid stool marker formulation comprising barium sulfate and a flocculant, wherein the amount of ionic dispersants in said solid stool marker formulation is less than 0.007 gram-equivalent weights of ionic dispersants per gram of barium sulfate. The present claims are not obvious over Mueller in view of Brown, and withdrawal of this rejection is respectfully requested.

Claims 1-10 and 19 are rejected as allegedly obvious over Mueller et al. in view of Brown and further in view of Ruddy U.S. 5,466,440. The Office Action states that neither Mueller nor Brown recite a particle size for barium sulfate, and that Ruddy teaches a barium sulfate formulation comprising a smectite clay, wherein the barium sulfate particle size is within the range claimed. Applicant notes that only claim 5 recites such a particle size, and therefore the relevance of Ruddy to the remaining claims was not specified in the Office Action.

Even if the use of high shear as disclosed in Ruddy were relevant to some limitations of the dependent claims, the combined teachings of Mueller, Brown, and Ruddy still do not teach or suggest the invention of claim 1, given the deficiencies of

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TEL. (617) 542-2290
FAX. (617) 451-0313

Mueller and the lack of any motivation to combine Mueller's liquid formulations with the solid formulations of Brown, as described above. It is further noted that Ruddy discloses only liquid formulations. Further deficiencies of Ruddy were discussed in the previous response. The withdrawal of this rejection is respectfully requested.

Claims 1-10 and 12-19 are rejected as allegedly obvious over Mueller et al. in view of Brown and further in view of Vining, U.S. 6,083,162. The Office Action states that Mueller and Brown do not disclose a method of visualizing the colon by administering the formulation and manipulating the data to determine the portion of the data due to marked stool to thereby provide a representation of the colon. Vining teaches a method of providing an interactive, three-dimensional rendering of a patient's colon.

Vining would appear to be relevant to certain limitations recited by claims 12-15; however, its relevance to the remaining claims was not stated in the Office Action. Claims 12-15 require administration of the formulation of claim 1. The combined teachings of Mueller, Brown, and Vining still do not teach or suggest the formulation of claim 1, given the deficiencies of Mueller and the lack of any motivation to combine Mueller's liquid formulations with the solid formulations of Brown, as described above. Therefore, the combined references do not teach every limitation of the present claims and do not render the claims obvious. The withdrawal of this rejection is respectfully requested.

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The Examiner is encouraged to telephone the undersigned attorney to discuss any matter which would expedite allowance of the present application.

Respectfully submitted,

KEVIN TAIT

By: _____
Charles L. Gagnebin III
Registration No. 25,467
Attorney for Applicant

WEINGARTEN, SCHURGIN,
GAGNEBIN & LEBOVICI LLP
Ten Post Office Square
Boston, MA 02109
Telephone: (617) 542-2290
Telecopier: (617) 451-0313

CLG:LJH/mrb

WEINGARTEN, SCHURGIN,
GAGNEBIN & LEBOVICI LLP
TEL. (617) 542-2290
FAX. (617) 451-0313

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APPENDIX

CALCULATION OF GRAM EQUIVALENT WEIGHTS OF IONIC MATERIAL IN MUELLER FORMULATION DUE TO BENTONITE

Typical Formula of bentonite:

$\{Al\ Fe_{1.67}\ Mg_{0.33}\ Si_4\ O_{10}\ (OH)_2\ \}^{3-}$ Na^+ Ca^{++}

Source: www.eytonsearth.org/clay-chemistry.php

Molecular Weight of this formula = 497.

Assuming that the only labile cations in the bentonite structure are Na and Ca (in acidic environments some Mg and Fe would also be unlocked from the structure and be available), then:

One Gram Equivalent Weight = Molecular Weight/3 = 166

In Mueller's formula, each gram of barium sulfate has at least 1.5g of bentonite (assuming 2% barium sulfate (highest value)and 3% bentonite (lowest value)).

Gram-equivalents of (ionic) bentonite per g of barium sulfate =

1.5/166 = 0.0090.

366685.1

WEINGARTEN, SCHURGIN,
GAGNEBIN & LEBOVICI LLP
TEL. (617) 542-2290
FAX. (617) 451-0313